Prognostic Factors of Clinical Outcome in Non-Paediatric Patients with Dengue Haemorrhagic Fever/Dengue Shock Syndrome


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Abstract
A total of 112 adults with dengue haemorrhagic fever (DHF) admitted at Clínica Santa Sofía, Caracas, Venezuela, were studied during June 1998–June 2001. Capillary leakage (CL) occurred in 28.8% cases, 21.6% experienced bleeding, 9.2% developed pleural effusion (PE) and 9.2% developed acute acalculous cholecystitis (AAC). High correlation was noticed between the length of illness prior to admission (IPA) and length of hospitalization (LH) and levels of Hct, Hb and leukocytes. Significant differences were seen in the length of IPA, LH and level of platelets for patients with or without bleeding (P<0.05) or CL (P<0.005), and in LH for patients with or without PE (P<0.005), or CL (P<0.05). Patients with AAC reached higher leukocyte counts (P<0.05). ANOVA showed an association between IPA and LH, between either of them and levels of Hb, Hct or leukocytes, and between platelets levels and PE, CL or bleeding. The length of IPA and degree of alteration of Hb, Hct, leukocytes and platelets predicted a more severe course in adults with DHF.

Keywords: Dengue, dengue haemorrhagic fever, adults, prognostic factors.

Introduction
Over the last decade, dengue fever has dramatically spread in virtually all Latin American and Caribbean countries which are infested with Aedes aegypti. During this period, the number of cases reported every year in these countries jumped from 250,000 to more than 750,000[1]. Furthermore, recent serological surveys suggest the occurrence of millions of such infections[2]. After its emergence in Cuba in 1981[3], epidemics or sporadic cases of dengue haemorrhagic fever (DHF) have been reported in at least 25 countries in the Americas[4]. Venezuela has recorded large numbers of DHF cases every year, and, in 1995, the country reported the largest outbreak in the region with almost 30,000 dengue cases and 5,000 DHF cases. Although DEN-1, DEN-2 and DEN-4 had been isolated during this epidemic, DEN-2 was the predominant serotype[5].

In contrast with observations made in Asian countries, where DHF is almost completely restricted to young children, in the Americas, older age groups are widely involved[6-8].

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The host’s immune response appears to be a major factor influencing the type and severity of disease, as sequential infection with different dengue virus serotypes in the presence of non-neutralizing antibodies has been strongly incriminated in the occurrence of DHF/DSS\textsuperscript{[8-10]}, and cases of DHF/DSS are seldom documented in patients with primary infection\textsuperscript{[11-13]}. Individual factors, such as age, sex, genetic background and underlying diseases, may also play a role\textsuperscript{[14]}. Since most of the currently available clinical and epidemiological data on DHF/DSS derives from observations on infected children, information is sparse regarding prognostic factors of poor evolution among adult patients. In an attempt to identify potential prognostic factors in this specific setting, a retrospective study was carried out among non-paediatric inpatients with DHF/DSS followed at a single South American private medical institution.

Materials and methods

A total of 112 non-paediatric patients (male/female ratio: 64/48; age range: 15-92 years; median 36 years) admitted to Clínica Santa Sofía, Caracas, Venezuela, during a 36-month period from June 1998 to June 2001, who were attended to by the same team of physicians, were included in the study. The endemic dengue transmission season in the country typically extends from May to October, matching the yearly cycle of rains.

All cases fulfilled the diagnostic criteria of DHF/DSS, according to WHO and PAHO definitions: acute febrile illness with evidence of bleeding, thrombocytopenia <10^5 per µL, and evidence of plasma extravasation, such as haemoconcentration (20% increase over base Hct, or 20% decrease after rehydration), polyserositis, or hypoproteinemia, with or without signs of circulatory failure, including narrowing of pulse pressure (≤ 20 mm Hg), hypotension, or shock\textsuperscript{[15]}. The level of severity of the condition was established according to the following scale:

(i) Grade I, fever + nonspecific constitutional symptoms + positive tourniquet test + evidence of haemoconcentration and thrombocytopenia;

(ii) Grade II, all of the above + spontaneous bleeding, usually restricted to the skin ± other sites;

(iii) Grade III, all of the above + circulatory failure manifested by rapid and weak pulse, narrowing of pulse pressure (20 mm Hg or less), or hypotension with the presence of cold, clammy skin, and restlessness or agitation, and

(iv) Grade IV, all of the above + profound shock with undetectable blood pressure and pulse\textsuperscript{[15]}.

Clinical evidence of gross capillary leakage (CL) was defined as the occurrence of polyserositis, expressed by any of the following: symptomatic pleural effusions, ascytis, pericardial effusions, gallbladder wall edema and/or acute acalculous cholecystitis.

Acute acalculous cholecystitis (AAC) was diagnosed according to the following criteria: fever; persistent abdominal pain; nausea and vomiting. On physical examination, occurrence of tenderness or muscle rigidity in the right upper abdominal quadrant, epigastrium, or both, and
Murphy's sign. Additional relevant findings were a palpable mass in the region of the gall-bladder, jaundice, and mild elevations in the serum levels of bilirubin, alkaline phosphatase, and/or transaminases. On ultrasound, demonstration of an enlarged gall-bladder with thickened wall (≥ 6 mm) and pericholecystic fluid appearing as a halo, or the presence of a diffuse, homogeneous, non-shadowing, medium level echogenicity within the gall-bladder lumen, were all considered ‘positive’ findings.\[16\]

Either specific IgM or IgG seroconversion over a period of 15 days was documented by means of a rapid commercial qualitative immunochromatographic test (PanBio Dengue®, Windsor, Australia).

Statistical analysis was performed using StatSoft, Inc. (1995), STATISTICA for Windows, Computer programme manual, Tulsa, OK. Either Student’s t-test for the comparison of means from independent samples of unknown variances, Pearson’s correlation analysis, univariate and multivariate logistic regression analysis was performed with CAA, vascular leakage or bleeding as main outcomes, by means of a forward stepwise independent variable entry in the final model. All calculations were two-tailed, and 0.05 significant criteria were used. ANOVA analysis of variables was performed as required.

**Results**

Out of 112 patients, 71 (63.4%) developed DHF grade I, 23 (20.5%) had DHF grade II, and 18 (16.1%) had either DHF grade III or grade IV. In 37 patients (33%), clinical signs of vascular leakage were evident, 25 (22.3%) experienced moderate to severe bleeding, and 14 (12.5%) developed pleural effusion on plain chest X-ray films. AAC ensued in 14 (12.5%) cases. No deaths occurred (Table 1).

### Table 1. Degree of severity of DHF and clinical complications in 112 non-paediatric Venezuelan patients

<table>
<thead>
<tr>
<th>Severity of disease and clinical complication</th>
<th>Number of cases</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHF grade I</td>
<td>71</td>
<td>63.4.9</td>
</tr>
<tr>
<td>DHF grade II</td>
<td>23</td>
<td>20.5</td>
</tr>
<tr>
<td>DHF grade III or IV</td>
<td>18</td>
<td>16.1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>25</td>
<td>22.3</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>14</td>
<td>12.5</td>
</tr>
<tr>
<td>Acalculous cholecystitis</td>
<td>14</td>
<td>12.5</td>
</tr>
</tbody>
</table>

Pearson’s correlation analysis results according to clinical complications are depicted in Table 2. A significant correlation was found between the levels of Hb and Hct (r = -0.762; P < 0.0001), and between the level of platelets and Hb (r = -0.280; P < 0.01). Correlation was also observed between the number of days of illness prior to admission (IPA) and the length of hospitalization (r = -0.233; P < 0.05), as well as between the length of hospitalization (LH) and the degree of alteration in platelets level (r = -0.198; P < 0.05). A higher correlation was seen between the length of hospitalization and the number of days of IPA (r = -0.426; P < 0.005) for patients with dengue grade II or higher, or those with bleeding (r = -0.427, P < 0.005).
Significant differences were seen in the length of IPA (mean 4.32 days vs. 3.60 days; P<0.05), and the minimum level of platelets (mean 43,000 per µL vs. 65,816 per µL; P<0.05) for patients with or without clinical bleeding, as well as those with or without dengue type 2 (mean 4.43 vs. 3.56 days, and 48,870 vs. 70,800 per µL; P<0.05, respectively). Significant differences were also found in the length of hospitalization (mean 5.77 days vs 3.61 days; P<0.005) for patients with or without pleural effusion, as well as for those with or without clinical vascular leakage (mean 4.85 days vs. 3.53 days; P<0.005). The length of IPA was longer (mean 4.35 days vs. 3.26 days; P<0.05), the length of hospitalization was longer (mean 4.85 days vs. 3.61 days; P<0.001), the serum levels of alkaline phosphatase were higher (mean 183 µL vs. 91 µL; P<0.05), and the minimum level of leukocytes was higher (mean 12,890 per µL vs. 5,026 per µL; P<0.001) in patients developing vascular leakage. Patients with AAC exhibited a significantly longer hospital stay (4.71 days vs. 3.71 days; P<0.05), and a higher mean level of peripheral blood leukocytes (15,986 x mm³ vs. 5,071 x mm³; P<0.001).

### Table 2. Significant differences in disease outcome in 112 non-paediatric Venezuelan patients with dengue haemorrhagic fever according to type of clinical complication

<table>
<thead>
<tr>
<th>Clinical complication</th>
<th>Variable</th>
<th>Mean value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bleeding</strong></td>
<td>Illness prior to admission</td>
<td>4.66 days 3.70 days</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>No</td>
<td>Minimum platelet level</td>
<td>43,619 per µL 61,128 per µL</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td><strong>Pleural effusion</strong></td>
<td>Length of hospitalization</td>
<td>5.0 days 3.6 days</td>
<td>P&lt;0.005</td>
</tr>
<tr>
<td>Yes</td>
<td>Illness prior to admission</td>
<td>4.24 days 3.53 days</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>No</td>
<td>Minimum platelet level</td>
<td>45,178 per µL 68,784 per µL</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td><strong>Signs of capillary leakage</strong></td>
<td>Length of hospitalization</td>
<td>4.71 days 3.56 days</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>Illness prior to admission</td>
<td>4.71 days 3.56 days</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>Minimum platelet level</td>
<td>45,178 per µL 68,784 per µL</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td><strong>AAC</strong></td>
<td>Peripheral blood leukocytes</td>
<td>11,300 per µL 3,418 per µL</td>
<td>P&lt;0.05</td>
</tr>
</tbody>
</table>

Both one-way and multivariate logistic regression analysis revealed that the only variables significantly associated with bleeding were illness severity on admission according to WHO scale (OR=5.3; P<0.001), and length of IPA (OR=1.7;
Prognostic Factors in Adult Patients with Haemorrhagic Dengue

P<0.05). Vascular leakage was also associated with illness severity on admission in the multivariate regression analysis (OR=14.3; P<0.005), as well as with the length of hospitalization (OR=1.79; P=0.001), illness severity on admission (OR=26.5; P=0.001), leukocytes level (OR=1.33; P=0.001), and a prolonged aPTTA† (OR=18.9; P=0.001), in the univariate regression analysis. Of note was the finding that whereas patients with bleeding did not remain hospitalized longer, those with vascular leakage did (OR=1.79; P=0.001). Statistically significant results for the one-way and multivariate logistic regression analysis are summarized in Tables 3, 4 and 5.

Table 3. Logistic regression analysis of clinical variables associated significantly with capillary leakage in 112 non-paediatric Venezuelan patients with dengue haemorrhagic fever

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>P</td>
</tr>
<tr>
<td>Degree of severity</td>
<td>26.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Length of hospitalization</td>
<td>1.79</td>
<td>0.001</td>
</tr>
<tr>
<td>Blood leucocytes level</td>
<td>1.33</td>
<td>0.001</td>
</tr>
<tr>
<td>Abnormal PTT</td>
<td>18.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Bleeding</td>
<td>3.51</td>
<td>0.015</td>
</tr>
</tbody>
</table>

OR = odds ratio
Blank cells indicate values that should not be included since they are not significant

† Activated partial thromboplastin time

Discussion

The age distribution for DHF cases in the Americas differs from that observed in South-East Asia[1,3,6,7,8,17,18], where young
children continue to be the age group almost exclusively affected. In contrast, an age range of 31 to 45 years has been reported for Brazilian patients with DHF/DSS[6], while in Puerto Rico, the mean age of the patients reported in 1990-91 was 38 years[7]. Furthermore, during the outbreaks in Cuba in 1981 and in Venezuela in 1989, about one third of the deaths were among patients older than 14 years[8,19], and in the 1997 Cuban outbreak, all registered deaths were seen among adults[8].

The main pathogenic feature of dengue is an increase in vascular permeability leading to loss of plasma from blood vessels, which causes haemococoncentration, low blood pressure and shock. This may also be accompanied by haemostatic abnormalities such as thrombocytopenia, vascular changes and coagulopathy[15].

The clinical spectrum of dengue virus infection may range from an asymptomatic infection to a severe and rapidly fatal disease[15,20-24]. The most severe end of the spectrum of dengue virus infection in children is represented by dengue shock syndrome (DSS)[15]. Adults seem less likely than children to suffer from DSS. Indeed, in a retrospective study of 108 adult Malaysians with DHF, the overall morbidity was significant (29.4%) but the case-fatality rate remained low (2.0%)[25].

Haemorrhagic manifestations in DHF usually consist of petechiae, ecchymoses, easy bruising and bleeding from venipuncture sites. Epistaxis, gum bleeding and gastrointestinal haemorrhage are less common[23-24]. If improperly treated, shock leads to metabolic acidosis, severe generalized bleeding and, eventually, death[23]. Unlike children, many adult patients show severe bleeding of the gastrointestinal (GI), or of other sites, preceding the shock, which may be severe enough to cause death[20,21,28].

Relevant laboratory findings in DHF cases include thrombocytopenia, haemococoncentration and hypoproteinemia[25]. A drop in platelet count to below 100,000 per µL and an increase of 20% or more in the haematocrit, both resulting from increased vascular permeability, are consistent findings. Other signs of plasma leakage include pleural effusion, ascites and hypoproteinemia. Leukopenia and leukocytosis are common, and aminotransferases are usually elevated. Thrombin, prothrombin and partial thromboplastin times are often prolonged. Fibrinogen levels decrease and fibrin degradation products may increase. In patients with DSS, the severity of laboratory abnormalities described for DHF tends to be worse. Dilutional hyponatremia and hypoproteinemia correlate with disease severity[25].

In the current series, patients with longer length of hospitalization exhibited significantly lower levels of platelets, as well as a higher tendency to severe capillary vascular leakage (CVL)[1]. Overall, a shorter duration of IPA associated surprisingly with a longer length of hospitalization, probably reflecting the fact that more severely ill patients tended to seek medical attention earlier. Nevertheless, patients with dengue type II, as well as those with evidence of CVL, exhibited significantly more protracted IPA. The occurrence of the latter two conditions most likely reflect the delay in

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1 CVL may induce many other clinical manifestations and complications besides clinical bleeding, such as pleural effusion, ascitis, joint swelling, etc.
initiating a proper and adequate fluid-replacement treatment, which is the key to treating DHF in order to compensate for the loss of plasma from blood vessels due to increased vascular permeability.[1,15]

Of note is the finding that a considerable percentage of the cases (12.5%) developed AAC. Recent data suggest that in children with DHF, a gall-bladder wall thickening =5 mm on ultrasonography correlates with a higher risk of hypovolemic shock[26]. However, despite a few scattered reports of AAC complicating adult DHF patients[27-30], little information exists in medical literature on the pathological and clinical implications of this newly recognized condition. It is worth mentioning that while our nine patients with AAC exhibited a significantly increased level of peripheral blood leukocytes during hospitalization, their clinical outcome in terms of IPA, length of hospitalization or occurrence of other life-threatening complications, did not differ from that of patients without AAC. Details of the clinical aspects and imaging techniques findings for this set of patients will be discussed elsewhere.

Viral, serological and genetic factors may influence virulence. Molecular studies have identified genetic variation among all 4 dengue virus serotypes[31-34]. Of note here is the finding that DEN-2 strains associated with grade II DHF or DSS grow to higher titers in peripheral blood leukocytes than do DEN-2 strains isolated from mildly ill patients[35,36]. Although characterization of the viral serotypes involved in these patients was not performed, DEN-1, 2 and 4 all circulated in Venezuela during the period when the cases occurred, DEN-2 being the most prevalent one[5].

In conclusion, the number of days of IPA, the length of hospitalization and the degree of alteration in the level of Hb, Hct, leukocytes and platelets were all predictors of a more severe and complicated course in adult patients with DHF/DSS. The onset of leukocytosis must suggest the occurrence of inflammatory complications such as AAC. DHF/DSS in the Americas continues to occur in a significant number of adults, but it is not clear whether this relates with the genetic background of the populations, the epidemiological events or, else, with other unknown factors.

References


